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SPONTANEOUS NEPHRITIS IN RABBITS AND ITS RELATION TO CHRONIC NEPHRITIS IN MAN

WITH ONE PLATE

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It is well known that spontaneous[1] nephritis is often found in rabbits, and there are frequent estimates in the literature as to its frequency. There is, however, not much detail published as to the finer structure and pathogenesis of this lesion, and it is still a serious source of error for those engaged in the study of experimental nephritis. It is noteworthy that no investigator who claims to have produced a chronic nephritis experimentally has been able to draw a sharp distinction between the spontaneous lesions and those supposedly produced by the experimental procedure. This fact is usually admitted, though sometimes ignored, and the argument is made that a lesion occurring much oftener in the experimental than in the control animals is due to the experimental procedure. It is not generally recognized that nephritis in animals (especially the rabbit) is entirely different in its pathogenesis from human chronic nephritis, and that therefore the successful experimental production of lesions of this character does not necessarily illuminate the problems of the etiology of human chronic nephritis. We have, therefore, thought it worth while to give a brief account of the etiology and pathogenesis of spontaneous nephritis and to call attention to its relations to the problems of human nephritis and experimental nephritis.

FREQUENCY

Smith[2] found some renal lesion in 11 of 50 rabbits. Ophüls,[3] in a study of the kidneys of 50 rabbits, found 28 entirely normal, 9 with slight parenchymatous lesions, 3 with a few small areas of cellular infiltration, and 10 with "scattered small areas in which were marked interstitial lesions with formation of small depressions on the surface."

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[1] "Naturally acquired," suggested by MacNider, is a more accurate term than "spontaneous," but the latter seems to be in general use.

[2] Arch. Int. Med., 1911, 8, p. 468.

[3] Proc. Soc. Exper. Biol. and Med., 1911, 8, p. 75.

Ghoreyeb[4] mentions a spontaneous lesion in 9 rabbits in an article in which 48 rabbits are recorded by number. Longcope[5] found lesions in the kidneys of 8 of 24 supposedly normal rabbits. Major[6] found that of "52 rabbits dead of natural causes, none had the extensive scarring of the cortex" such as was found in his experimental animals. Apparently Major was writing only of severe lesions.

In our own experience, which includes the study of over 200 rabbits over a period of two years, the percentage with spontaneous nephritis varied greatly from month to month. Sometimes nearly all were found normal, but usually from 10-20% were diseased. There were two periods during the past two years, each lasting about 1 month, when over 80% of the rabbits examined had nephritis. The disease apparently assumes an endemic form at times. The animals used were purchased in large groups from different dealers, and it was noted that the disease was much more prevalent in some groups than in others when they were first put into the animal house. Many rabbits developed nephritis after they came into our possession.

In view of the great variations we have noted, it seems unsafe to conclude, as Longcope and others have done, that a given lesion is due to the experimental procedure merely because it occurs oftener in the experimental than in the control animals. The source of the animals used as controls and the length of time they are kept in the animal house are very important factors.

ETIOLOGY

We have attempted to isolate bacteria in eight cases of spontaneous nephritis by removing pieces of the kidney aseptically immediately after the animal had been killed, or from the living animal under ether anesthesia. The pieces of tissue were put in plain broth or in dextrose broth. Signs of growth first appeared in the medium after several days' incubation. Four of the cases gave no growth. In two cases we obtained a gram-positive staphylococcus in pure culture. These organisms when first isolated were very virulent — ¼ c c of a broth culture being a fatal dose for a rabbit. The third subculture, however, was practically avirulent.

In two other cases pure cultures of streptococci were obtained. These grew feebly and did not cause death or infection when inoculated into rabbits. We did not succeed in reproducing nephritis by injecting normal rabbits with the organisms obtained from any of the diseased kidneys. In the absence of this evidence the organisms isolated cannot with certainty be regarded as the etiologic agents; but it seems to us a highly probable assumption. They can hardly be due to contamination since the growth did not appear until after several days' incubation, the organisms were in pure culture, and in two instances were very virulent. It is known to us that streptococci have often been obtained from the tissues of rabbits, but these have usually been from animals that died slowly from natural or experimental disease where the opportunity for agonal invasion was present, and not from animals killed and cultured directly. Dr. W. P. Larson of this laboratory tells us that he has repeatedly found the normal kidneys of rabbits sterile.

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[4] Jour. Exper. Med., 1913, 18, p. 29.

[5] Ibid., 1913, 18 p. 678.

[6] Jour. Med. Research, 1917, 35, p. 349.

PATHOLOGICAL ANATOMY AND GENESIS

For the sake of clearness we shall discuss this topic without special reference to observations recorded in the literature. In the earliest stages small foci of lymphocytes are found usually near the corticomedullary junction but sometimes elsewhere in the cortex. There are only a few of these lymphocytic foci in mild cases — many sections of the kidney may be entirely normal. But in severe cases these areas are numerous, and they may fuse to form extensive areas of infiltration. The lymphocytes are of intermediate size and lie for the most part closely packed between the tubules, but a few invade the epithelial cells (Fig. 1). At this early stage there are no gross changes on the surfaces of the kidneys. In severe cases the cut surface is clouded. Albumin is present in the urine except in cases where the foci are few and small.

The pressure of the exudate soon causes atrophy and disintegration of the parts of the tubules involved in the lymphocytic foci, and the destruction of these tubules is responsible for the changes that occur subsequently. The first gross changes noted are the appearance of a reddish or purplish spot on the surface of the kidney overlying the lymphocytic focus. Later on this purplish spot gradually sinks and a distinct funnel-shaped depression develops in its place. In the final stages the pit may be as deep as the thickness of the cortex. When the surfaces are studded with such deep pits the kidney assumes a shrunken scarred appearance (Fig. 2).

Microscopic sections through the purplish surface spot before the pit has developed show an early stage of atrophy of the cortical tubules belonging to the tubules destroyed in the lymphocytic foci. The atrophic tubules are smaller and more darkly stained than the normal, and their lumens are small or completely obliterated (Fig. 3). As the atrophy progresses these tubules become gradually converted into narrow epithelial cords, and in the final stages even these have disappeared entirely. Sections through pits such as are shown in Fig. 2 show complete atrophy of the tubules, but the shrunken glomeruli are easily identified (Fig. 5).

The tubules atrophy from the lymphocytic focus to the tip of the medullary pyramid as well as toward the surface of the kidney. This is easily seen by the study of serial sections of such a kidney as is shown in Fig. 2. The scar is readily traced from the surface pit down through the medulla to the tip of the pyramid. In the medulla it stands out very prominently as a band of tissue from which the tubules have disappeared (Fig. 4). The end-result of the lymphocytic infiltration at the cortico-medullary junction is the formation of a wedge-shaped scar with its apex at the tip of the pyramid and its base at the surface of the kidney. The lymphocytes usually occur only near the center of the wedge. That this is the shape of the lesion can be determined in any case by the study of serial sections.

We are not dealing therefore with a diffuse interstitial nephritis such as occurs in diphtheria and scarlet fever, but with discrete lymphocytic foci which cause atrophy of the entire tubule system by destroying its central portions. In severe cases where the foci fuse the appearance of acute interstitial nephritis is simulated.

The gross appearance of the kidneys in the late stages depends on the number of lymphocytic foci originally present. There may be only 2 or 3 pits, or the pits may be so closely set that the kidney has a shrunken contracted appearance. These severe extensive cases have given rise to the view that spontaneous nephritis in the rabbit is comparable to the contracted kidney of man, but this is not a correct interpretation. The most common form of chronic nephritis in man is a glomerulo-nephritis in which the primary injury is to the glomerulus, and the atrophy of the tubule is subsequent to the destruction of this structure. In the human arteriosclerotic kidney areas of tissue, of small or large size, undergo atrophy because of sclerosis of the nutrient artery. In spontaneous nephritis in the rabbit neither of these conditions obtains, but the atrophy results from destruction of a part of the tubule by an inflammatory exudate. The only form of human nephritis in any way comparable to rabbit nephritis is a form of focal infection in the kidney characterized by abscesses or diffuse inflammatory areas, and due to hematogenous infection. It is often referred to as "excretory" nephritis, or excretory pyelonephritis when the infection passes on into the pelvis of the ureter.

It is clear, therefore, that the successful solution of the problem of spontaneous nephritis in the rabbit will not necessarily throw any light on the problems of human nephritis. As far as we have observed spontaneous nephritis in animals other than the rabbit is similar to rabbit nephritis, but we have not studied other animals extensively enough to warrant a general statement. Le Count[7] described a case of chronic glomerulo-nephritis in a rabbit, and MacNider[8] reported this form as common in dogs. The important problem for experimental pathology in this connection is the production of a chronic glomerulo-nephritis.

Spontaneous nephritis frequently results in recovery. This is especially true in cases where the infection is not very extensive. Albumen disappears from the urine and the functional test is normal, but the pits on the surface persist. There is no attempt at regeneration of the scar tissue. In many cases, however, there is a progressive destruction of renal tissue. Death usually results from toxemia and intercurrent diseases rather than from renal insufficiency.

URINARY FINDINGS

Albuminuria is usually demonstrable in the active stages of the disease. It may be intermittently present in mild cases, and it disappears entirely after healing. This last point is of considerable importance in experimental work. We have found deeply pitted and scarred kidneys at operation in several animals which had normal urine and normal phthalein excretion just before the operation. The presence of albumin in the urine does not necessarily mean that the rabbit has nephritis of the type described above. Our records show seven animals with albuminuria in which necropsy revealed only slight tubular injury in the kidney, the cause of which could not be clearly established. It is well known that albuminuria may be produced by a large variety of renal irritants. Casts are not constantly present.

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[7] Jour. Infec. Dis., 1914, 15, p. 389.

[8] Jour. Med. Research, 1916, 34, p. 177.

RENAL FUNCTION

The phenolsulphonephthalein test shows no change except in severe cases. The lowest 2-hour excretion we have recorded is 20%. When the phthalein test was reduced to any considerable degree extensive renal involvement was always present. Healed cases gave a high excretion, even though the scarring was considerable.

DEVELOPMENT OF NEPHRITIS IN CONTROL ANIMALS

We have records of two rabbits with normal urine in which exploratory operation showed the surfaces of the kidneys smooth. These animals were kept as controls for some other experiments. About three months after the exploratory operation they were found to have developed a typical spontaneous nephritis. This observation is of great importance in interpreting experimental results. It is easily possible for nephritis to develop during the course of long experiments independently of the experimental procedure.

Another type of lesion occasionally seen has been described by several authors (Le Count,[7] Fig. 11, p. 402). It consists of a wedge-shaped area composed of dilated tubules with flattened epithelium. We have not worked out the genesis of this lesion.

ASSOCIATED LESIONS

In all cases of spontaneous nephritis there was an associated lymphocytic infiltration of the portal connective tissue of the liver. This chronic hepatitis is also present in many cases in which the kidneys are normal. About 75% of the livers examined by us (50 cases) showed portal infiltration in varying degrees. Organisms may usually be cultivated from these livers but they do not always correspond with those obtained from the kidneys.

We did not make an extensive routine examination of the heart muscles in our nephritic cases; but in three rabbits in which large numbers of sections of heart muscles were examined we found foci of lymphocytes similar to those described by Longcope[9] and attributed by him to the action of foreign protein. It is probable that this form of myocardial infection is frequently associated with spontaneous nephritis.

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[9] Jour. Exper. Med., 1915, 22, p. 793.

RELATION OF SPONTANEOUS TO EXPERIMENTAL NEPHRITIS

There has been no confusion of spontaneous with experimental acute nephritis since the two lesions are entirely different; but the natural disease has seldom if ever been sharply differentiated from chronic lesions supposedly produced by experimentation. As indicated in preceding paragraphs no observer has offered any convincing evidence that the lesion supposedly produced differs anatomically from the spontaneous disease. In fact, the illustrations accompanying many articles correspond entirely with the appearances of the natural disease. The usual argument is that a lesion occurring much oftener in experimental than in control animals must be due to the experimental procedure (O'Hare;[10] Dickson;[11] Christian, Smith and Walker;[2] Longcope[12]). But other explanations of these results are possible. 1. A spontaneous nephritis may develop during the course of experiments lasting several months. The control animals were not kept in the laboratory for the same length of time under the same conditions. Klotz[13] admits this as a possible source of error in his work. 2. The use of renal irritants such as uranium nitrate may favor the development of an infection in the kidneys, because of the general lowered resistance caused by the drug or because injured renal tissue is more susceptible than normal. The investigators who used uranium did not make cultures of the kidneys to see if bacteria were present. We obtained a growth of bacteria from one uranium kidney.

Observers who apparently did not examine the urine at the beginning of each experiment, and there are several in this group, are open to the criticism that the animals may have had nephritis at the outset of the experiment.

When virulent bacteria were injected into the blood stream, as in the experiments of Le Count,[7] Klotz,[13] and Hartzell and Henrici[14] it is easily possible that they are entirely responsible for the resulting lesions. One would expect a lesion resembling spontaneous nephritis from this procedure. The acute glomerular lesions obtained with streptococci suggest a relationship between these organisms and human glomerulo-nephritis; but the other lesions which various experimenters have attributed to injected bacteria bear no anatomic resemblance to the human disease.

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[10] Arch. Int. Med., 1913, 12, p. 49.

[11] Ibid., 1909, 3, p. 375.

[12] Jour. Exper. Med., 1913, 18, p. 678.

[13] Trans. Assn. Am. Phys., 1914, 29, p. 49.

[14] Jour. Am. Med. Assn., 1915, 64, p. 1055.

SUMMARY

Spontaneous nephritis in the rabbit is a subacute or chronic infectious disease characterized in the early stages by lymphocytic infiltrations in the kidneys usually at or near the cortico-medullary junction.

The parts of the tubules included in each lymphocytic focus undergo atrophy, and subsequently there is atrophy of the tubule systems both proximally and distally to the lymphocytic foci. The end-result is the formation of wedge-shaped scars with their apices at the apex of the pyramid and their bases formed by pits on the surface.

In our experience nephritis is much more common in some groups of rabbits than in others. The sanitary environment seems to be important. The disease is especially apt to develop in animals kept in the laboratory for several months.

Albuminuria is present in the active stages of the disease, but is absent in healed cases. Unlike human chronic nephritis many cases recover.

The investigators who believe they have produced chronic nephritis experimentally have not had controls adequate to exclude the spontaneous disease, and the lesions described correspond closely with spontaneous lesions.

No chronic glomerulo-nephritis has been produced experimentally. There is no anatomic or pathogenetic relationship between spontaneous nephritis in the rabbit and human chronic glomerulonephritis.

EXPLANATION OF PLATE

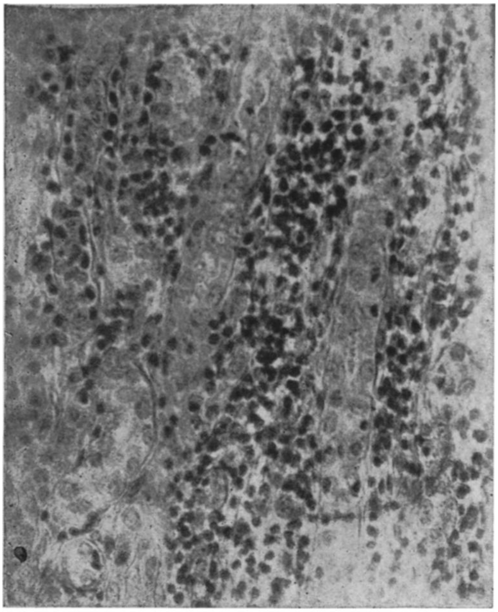
Fig. 1.—Photomicrograph. Area of lymphocytic infiltration at the cortico-medullary junction. Some tubules are already destroyed. This is the earliest type of lesion in spontaneous nephritis.

Fig. 2.—Photograph. Kidney showing numerous deep pits due to atrophy of cortical areas. The atrophic areas were produced by lymphocytic infiltrations at the cortico-medullary junction.

Fig. 3.—Early stage of atrophy of convoluted tubules due to destruction of their corresponding collecting tubules in a lymphocytic focus at the edge of the medulla. (The tubules in the lower left hand part of the figure are normal.)

Fig. 4.—Scar in medulla. This was traced in serial sections and found to connect with a surface pit such as is shown in Fig. 5.

Fig. 5.—Cortical pit (scar) showing complete disappearance of all the tubules. The glomeruli are still present. This is a healed lesion.



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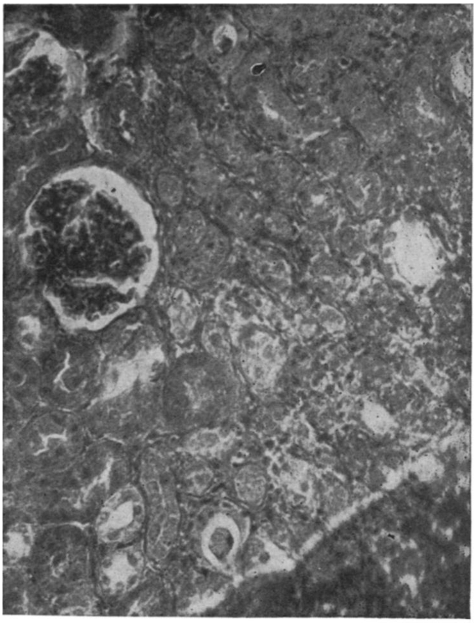

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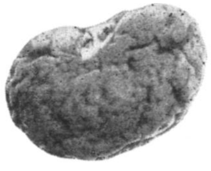

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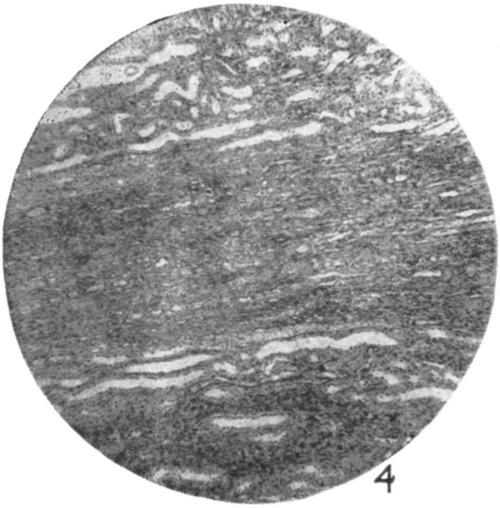

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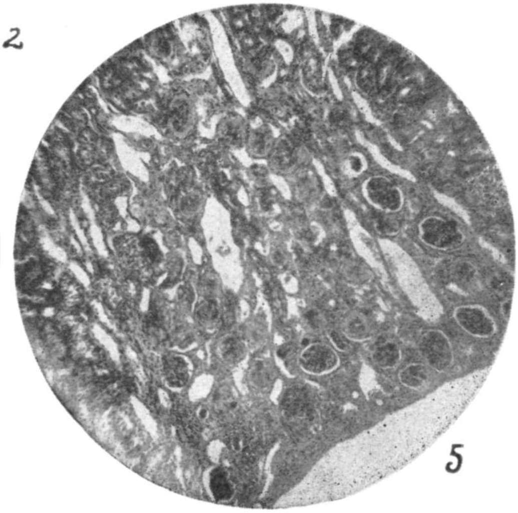

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